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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,242	07/30/2001	Stephen C. Ekker	09512/033003	2274

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EXAMINER	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/918,242	EKKER ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-67* is/are pending in the application.

4a) Of the above claim(s) *1-20,24-58 and 65-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-23 and 59-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 9,15
4)☐ Interview Summary (PTO-413) Paper No(s). _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: _____

DETAILED ACTION

1. This Action is in response to the communication filed on 12/16/02, as Paper No. 13. Claims 1-67 are currently pending in the application and are addressed herein.

Election/Restrictions

2. Applicant's election with traverse of Group II (claims 21-23 and 59-64) in Paper No. 13 is acknowledged. The traversal is on the ground(s) that 1) Groups I and II are a product and a process of making the product, but applicants argue that the product can not be made by a different method, 2) Groups I and IV are a product and process of using the product, but applicants argue that process can not be performed with another product; and 3) Groups II and IV are related. This is not found persuasive because 1) Groups I and II are a product and a process of making the product. It is pointed out that there are different ways that the product could be made. For instance, antisense molecules could be to inhibit the expression of the target genes in the embryos or a vector which expresses specific antisense molecules could be used. Furthermore, double stranded RNAi molecules could be used as well as ribozymes or PNAs. Therefore there are a number of different ways that the product could be made and the restriction is proper. 2) Groups I and IV are a product and process of using the product. It is pointed out that not only can the process be used with different products (i.e. embryos with different comprising different inhibitory molecules, such as those mentioned above), but the product could also be used in materially different processes. For instance, the embryos could be used to

using the product (I and IV) are patently distinct and restriction is proper. 3) Groups II and IV are not related because they are two distinct processes with different starting materials, different method steps and different desired outcomes. For instance the goal of invention II is to make a teleost embryo comprising a polynucleotide analogue wherein the polynucleotide analogue reduces the expression of a target gene. This requires starting with an embryo that expresses a target nucleic acid, and then steps that include transferring a polynucleotide analogue to said embryo. The goal of invention IV is to determine the phenotype of associated with a target nucleic acid sequence. This requires starting with an embryo that has the expression of the targeted nucleic acid inhibited, and requires steps that include assaying the physiological develop of the embryo. The goal of IV is to identify the development phenotype associated with a particular nucleic acid. Therefore, the claims are patentably distinct and the restriction is proper. The Examiner would like to thank Applicants for noticing that claims 56-58 were not properly grouped and pointing out that these claims should be included in Group VII. Claims 56-58 are now grouped in Group VII, as suggested by Applicants. Furthermore, a serious burden exists to search the different groups, as evidenced by the different classifications of the Groups.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-20, 24-58 and 65-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13. Claims 21-23 and 59-63 are examined herein.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 21-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are very broad and encompass inhibiting the expression of any target nucleic acid (such as any mRNA) in any teleost embryo that undergoes meroblastic cleavage using any polynucleotide analogue.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164).

Here, the claims encompass targeting any nucleic acid (such as mRNA) in a teleost embryo using any polynucleotide analogue targeted to the nucleic acid. However the

expressed post-embryonic teleost tissue. In order for the method to work, one of skill in the art would have to know which nucleic acids were present in the embryos. Without a clear indication which nucleic acids (e.g. mRNAs) are present in the embryo, one of skill in the art would not be able to design the polynucleotide analogues and would not be able to reduce the expression of the target nucleic acid. The specification only describes the use of modified morpholinos (as polynucleotide analogues) and has only describe a few target nucleic acids which are present in the developing teleost embryo (e.g., vegf, frizzled, chordin, and Tsg). Considering all of the nucleic acids which are expressed during teleost embryonic development, the specification has not adequately described a sufficient number of target nucleic acids or polynucleotide analogues.

6. Claims 21-23 are also rejected under 35 U.S.C. 112, first paragraph (in view of the written description rejection above), as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As mentioned above, the claims encompass a large number of target nucleic acids and a large number of polynucleotide analogues. However, the specification has not adequately described a sufficient number of these molecules. Without a clear indication of which nucleic acids are expressed in the developing teleost embryo, one of skill in the art would not know how to make and use the invention without performing an undue amount of additional experimentation. Furthermore one of skill in the art would not know which polynucleotide

7. Claims 59-64 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of reducing expression of a selected nucleic acid in an animal by administering at least two polynucleotide analogues that are that are complimentary to different regions of the target nucleic acid, wherein the at least two polynucleotides are more effective at reducing expression than either alone, and encompass synergistic effects of the at least two polynucleotides (compared to one polynucleotide alone). Therefore the claims encompass any two polynucleotides which are complimentary to different regions of any target nucleic acid and which have a synergistic effect when used in combination. This would potentially encompass millions of different polynucleotides considering every possible polynucleotides that could be designed for every possible target nucleic acid, and includes molecules for which there is insufficient description provided in the specification.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show

Here, the claims encompass any two polynucleotides which are complimentary to different regions of any target nucleic acid and which have a synergistic effect when used together. However, the specification has not identified how to design and make synergistic antisense polynucleotides to any target nucleic acid of interest. There is no indication of which regions of any target nucleic acid can be targeted by polynucleotides and consistently result in a synergistic inhibition of target gene expression. Furthermore, there is not a sufficient description of a representative number of species disclosed in the specification.

In the application at the time of filing, there is no record or description which would demonstrate conception of any polynucleotide analogues which have synergistic effect when used in combination. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not sufficiently described in the specification.

8. Claims 59-64 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In view of the written description rejection above, the claims potentially encompass Millions of different polynucleotide analogues considering every possible polynucleotide analogue that could be complementary to every sequence of every gene of interest. However, the specification has not sufficiently described the polynucleotide analogues which would have

sufficient description of molecules encompassed by the claims, on of skill in the art would not know how to make or use the invention without performing an undue amount of additional experimentation.

9. It is critical for the practitioner to know which target nucleic acids are present in the embryo and when they are present because if the target is a mRNA and it is not known when the mRNA is present in the embryo, one of skill in the art would not know when to administer the polynucleotide analogues such that the administration would result in an inhibition of expression of the target nucleic acid.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Barabino et al (Mech. Develop. 1997, 63:133-143. Listed in IDS as reference AJ).

It is noted that the claims are very broad and encompass administering any polynucleotides analogue (such as an antisense polynucleotide) to any teleost embryo that

Barabino teaches a method for producing a teleost embryo comprising a polynucleotide analogue, wherein said teleost embryo is a zebra fish embryo (which undergoes meroblastic cleavage) and wherein the polynucleotide analogue is present in an amount effective to reduce expression of a target nucleic acid in the embryo, by contacting the embryo with the polynucleotide.

Specifically, Barabino teaches using antisense oligonucleotides that are specific for the Alx gene (see abstract and p. 138, first column). The zebra fish embryos were cultured in the presence of the antisense oligonucleotides, therefore, the antisense molecules were added to the surface of the embryos (see pg. 138, first column).

12. Claim 59 is rejected under 35 U.S.C. 102(b) as being anticipated by Reed (US Patent 5,734,033, issued 3/31/1998).

It is noted that the claim is very broad and encompasses a method for reducing the expression of any selected nucleic acid in any animal comprising contacting the animal with at least two polynucleotide analogues that are complimentary to different regions of the target nucleic acid, wherein the at least two polynucleotides are more effective at reducing expression than either alone.

Reed teaches antisense oligonucleotides that are targeted to the human Bcl-2 gene, and can be used to inhibit the expression of Bcl-2 in human cells (see abstract). Reed indicates that

molecules specific for different region of the bcl-2 mRNA: the translation initiation antisense (TI-AS), the splice donor antisense (SD-AS), and the splice acceptor antisense (SA-AS) (e.g., see Table 1). Reed specifically teaches that any combination or subcombination of nucleotides complimentary or substantially complimentary to the bcl-2 mRNA that inhibit cell proliferation is suitable for use in the invention (see col. 4, lines 25-32). Reed also teaches that the oligodeoxynucleotides may be administered to patients as a combination of two or more different antisense oligodeoxynucleotide sequences or as a single type of sequence. For instance, TI-AS and SD-AS could be administered to patient or TI-AS alone. It would be expected that the combination of two or more oligodeoxynucleotides would be a more effective treatment than the administration of a single oligo. (e.g., see col. 6, lines 34-38).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claim 59 and 64 is rejected under 35 U.S.C. 103(a) as being unpatentable over Reed (US Patent 5,734,033, issued 3/31/1998) in view of Summerton et al. (Antisense & Nucl. Acid Drug Develop. Vol. 7, p. 187-195; 1997, listed in IDS as reference AYYYY).

As mentioned above Reed teaches antisense oligonucleotides that are targeted to the human Bcl-2 gene, and can be used to inhibit the expression of Bcl-2 in human cells (see abstract). Reed indicates that the method is useful for treating cancers such as certain lymphomas which are characterized by an overexpression of bcl-2 (see col. 1, lines 39-51). Reed teaches three different antisense molecules specific for different region of the bcl-2 mRNA: the translation initiation antisense (TI-AS), the splice donor antisense (SD-AS), and the splice acceptor antisense (SA-AS) (e.g., see Table 1). Reed specifically teaches that any combination or subcombination of nucleotides complimentary or substantially complimentary to the bcl-2 mRNA that inhibit cell proliferation is suitable for use in the invention (see col. 4, lines 25-32). Reed also teaches that the oligodeoxynucleotides may be administered to patients as a combination of two or more different antisense oligodeoxynucleotide sequences or as a single type of sequence. For instance, TI-AS and SD-AS could be administered to patient or TI-AS alone. It would be expected that the combination of two or more oligodeoxynucleotides would be a more effective treatment than the administration of a single oligo. (e.g., see col. 6, lines 34-38).

Summerton teaches morpholino modified oligonucleotides which are novel antisense structures that solve the sequence specificity problems associated with antisense oligos and provides high and predictable activity in cells. Summerton teaches that the morpholino oligos also exhibit little or no non-antisense activity, afford good water solubility, are immune to nucleases and are designed to have low production costs (see abstract)

Therefore, it would have been prima facie obvious to one of skill in the art at the time of filing to modify the method of reducing bcl-2 expression in a patient (taught by Reed) by modifying the antisense oligonucleotides into morpholino modified oligonucleotides.

One of ordinary skill in the art would have been motivated to change the antisense oligos into morpholino modified oligos because it would have been more cost effective, it would have increased the half-life of the oligos (probably resulting in better results), and would have decreased any non-antisense activity.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
March 10, 2003